

REMARKS

Claims 1 and 3-46 are pending in the present application.

The rejection of Claims 1-2, 8-11, 12, 16, and 17 under 35 U.S.C. §102(b) over Eritja et al, is obviated by amendment.

The examined claims of the present application contain 2 independent composition of matter claims - Claims 1 and 30. These independent claims will be discussed individually as follows:

Claim 1:

Claim 1 relates to a compound according to formula (1), notably wherein the radical  $R^2$  is an aromatic radical. The compounds according to claim 1 are suitable for use in a method using light-controlled synthesis of oligonucleotides. The examiner alleges that Eritja et al anticipates the claimed invention. Applicants disagree.

In Eritja et al, no light-controlled method for oligonucleotide synthesis is described. Instead, the protective group in Eritja et al is cleaved off by means of DBU (see page 4174, lines 1 to 2 and 8 to 9).

More importantly, Eritja et al exclusively discloses compounds in which the radical  $R^2$  (nomenclature according to the present application) is a hydrogen atom. In contrast, the compounds in pending Claim 1 require that  $R^2$  is an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted aroyl group. No compounds meeting this requirement are disclosed in Eritja et al. Therefore, Claim 1 is novel in view of Eritja et al.

Claim 30:

Eritja et al exclusively disclose compounds in which the radical  $R^4$  (nomenclature according to the present application) is a hydrogen atom. The compounds according to the new Claim 30 require  $R^4$  to be  $OCH_3$  or an optionally substituted alkyl group containing up to 4 carbon atoms. Such compounds are not disclosed in Eritja et al. Therefore, Claim 30 is novel in view of Eritja et al.

The: (a) rejection of Claims 1-17 under 35 U.S.C. §103(a) over US 5,763,599 (Pfleiderer et al), and (b) the obviousness-type double patenting rejection of Claims 1-17 over Claims 1-14 of US 5,763,599 (Pfleiderer et al), are obviated in part by amendment and traversed in part.

At the outset, with respect to Claim 1, Applicants submit that Pfleiderer et al exclusively disclose compounds in which  $R^2$  (nomenclature according to the present application) is equal to H or  $OCH_3$ . In contrast, the compounds in pending Claim 1 require that  $R^2$  is an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted aroyl group. No compounds meeting this requirement are disclosed in Pfleiderer et al. Therefore, Claim 1 is novel in view of Pfleiderer et al. Moreover, Pfleiderer et al offers no motivation to modify their disclosed compounds to arrive at the compounds as presently claimed in Claim 1 (and the claims dependent therefrom). Accordingly, the disclosure and the claims of Pfleiderer et al fail to render the claimed invention in Claim 1 (and the claims dependent therefrom) obvious.

Similarly, with respect to Claim 30, it should be noted that Pfleiderer et al merely discloses compounds in which  $R^1$  (nomenclature according to the present application) is equal to H,  $OCH_3$ ,  $NO_2$  or CN. In contrast, the compounds according to the new Claim 30

require R<sup>1</sup> to be COOY. Such compounds are not disclosed in Pfleiderer et al. Therefore, Claim 30 is novel in view of Pfleiderer et al. Moreover, Pfleiderer et al. offers no motivation to modify their disclosed compounds to arrive at the compounds as presently claimed in Claim 30 (and the claims dependent therefrom). Accordingly, the disclosure and the claims of Pfleiderer et al. fail to render the claimed invention in Claim 30 (and the claims dependent therefrom) obvious.

Further, Applicants wish to direct the Examiner's attention to a publication of Hasan and Pfleiderer et al. in Tetrahedron, Vol. 53, No. 12, 1997, pages 4247 to 4264 (referred to herein as "Hasan et al."; copy **submitted herewith** and listed on a Form PTO-1449).

Hasan et al. has the same content as Pfleiderer et al., but provides somewhat more accurate and more extensive information on the properties of the compounds disclosed in Pfleiderer et al. and Hasan et al. Of most relevance is the last sentence in the abstract of Hasan et al. In view of this disclosure and the position taken by the Examiner with respect to Pfleiderer et al., Hasan et al. is submitted herewith along with an explanation as to why the claimed invention is not obvious in view of Hasan et al. or Pfleiderer et al.

Hasan et al. disclose the same compounds as Pfleiderer et al. as apparent by comparing the table in Pfleiderer et al. from the bottom of column 24 to the top of column 25 with table 1 on page 4251 of Hasan et al. Therefore, for the same reasons as given above, Applicants submit that the claimed invention is novel and not obvious in view of the disclosures of Hasan et al. and Pfleiderer et al. However, the following additional distinctions warrant mention.

Hasan et al. discloses a method in which NPPOC protective groups are cleaved off photolytically. These NPPOC protective groups differ in the radicals R<sup>1</sup> (designation in

Hasan et al = R<sup>3</sup>) and R<sup>2</sup> from the protective groups according to Claims 1 and 30 of the present application.

As stated above for Pfleiderer et al, in Claim 1 of the present applicaiton, R<sup>2</sup> is an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted aroyl group. In contrast, R<sup>2</sup> in Hasan et al = H or OCH<sub>3</sub>.

Also as stated above for Pfleiderer et al, in Claim 30 of the present application, R<sup>1</sup> (designation in Hasan et al = R<sup>3</sup>) is equal to COOY. In contrast, R<sup>1</sup> (designation in Pfleiderer et al = R<sup>3</sup>) in Hasan et al is H, Cl or OCH<sub>3</sub>.

Neither COOY groups nor aryl, heteroaryl or aroyl groups are disclosed or made obvious as R<sup>1</sup> or R<sup>2</sup> in Pfleiderer et al or Hasan et al.

Tables 1 to 4 on pages 51 to 53 of the present application contain a *direct* comparison of the inventive protective groups with a protective group according to Pfleiderer et al or Hasan et al. The protective group designated as compound No. 26 in the present application corresponds to compound 36 in Hasan et al (compound 10 in Pfleiderer et al). Thus, according to Table 1 of Hasan et al, it is the protective group with the best half life of all protective groups disclosed in Hasan et al.

For the case of cleaving the protective groups off by photolysis – both in solution and under dry conditions - Tables 1 to 4 of the present application show that the inventive protective groups whose radical R<sup>2</sup> differs from those of Pfleiderer et al or Hasan et al have half lives that are one half or only one third as long as those of the protective groups of Pfleiderer et al or Hasan et al. This proves that the deprotection time has been accelerated by a factor of 2 to 3 compared with Pfleiderer et al or Hasan et al by the introduction of an aromatic radical at R<sup>2</sup>.

Table 5 of the present application shows that 86% yields were attained after as little as

18 seconds even in the dry system by using a protective group (Bz-NPPOC) modified at R<sup>2</sup> in the manner of the invention. In contrast, the NPPOC protective group according to Hasan et al, or in other words compound 36, led only to 81% conversion after 65 seconds. This proves the considerable technical advance of the new protective groups containing a specific R<sup>2</sup> radical.

Not only during deprotection under dry conditions and during deprotection in solution but also during deprotection in support-bound systems. Therefore, the protective groups according to Claim 1 of the present application exhibit much faster deprotection times than do those from Pfleiderer et al or Hasan et al.

Proof that the protective groups according to Claim 30 of the present application containing R<sup>1</sup> = COOY also bring about a considerable technical advance compared with Pfleiderer et al or Hasan et al can be seen by referring to Fig. 3 of the present application. Accordingly, a protective group according to Claim 30, in which R<sup>1</sup> was changed compared with Pfleiderer et al or Hasan et al and deprotected by irradiation under dry conditions, or in other words without solvent, exhibits a much improved yield. The protective groups compared in Fig. 3 include, among others, 5'-MeC-NPPOC-dt (according to Claim 30 of the present application) and 5'-NPPOC-dT (corresponds to Pfleiderer et al and Hasan et al). Fig. 3 shows that the inventive 5'-MeC-NPPOC-dt protective group leads to a deprotection yield of 82% after as little as 20 seconds, whereas never more than a 57% deprotection yield could be achieved even after 1 minute with the protective group from Pfleiderer et al or Hasan et al (5'-NPPOC-dT). Thus the protective group according to Claim 30 not only is better in deprotection time but also is drastically better in absolute deprotection yield.

A comparable experiment with a support-bound protected desoxythymidine (see Fig. 5 of the present application) yielded 85% conversion after 11 seconds in the case of the

inventive t-BuC-NPPOC-dT (compound 25), whereas comparable conversion could be achieved with non-inventive MeNPOC-dT (prior art protective group) only after 29 seconds.

Figs. 3 and 5 as well as Tables 1 to 5 therefore show that the inventive protective groups containing radicals  $R^1$  or  $R^2$  (nomenclature according to the invention) changed by comparison with Pfleiderer et al and Hasan et al represent a considerable technical advance in photolysis in a dry system. This technical advance is manifested by much higher yields accompanied at the same time by much shorter half lives.

Tables 1 to 4 of the invention show further that the inventive protective groups modified at  $R^2$  also exhibit a considerable technical advance compared with Pfleiderer et al or [missing: Hasan et al] during photolyses in solution.

Starting from Pfleiderer et al or Hasan et al as the closest prior art, the objective problem of the present application must be regarded as providing protective groups that can be cleaved off more rapidly and at the same time lead to higher yields, especially in the dry system:

The solution of this problem, or in other words the introduction of COOY groups at  $R^1$  or of aromatic groups at  $R^2$ , is based on careful deliberations and is not made obvious by Pfleiderer et al or Hasan et al.

Thus Hasan et al discloses on page 4251, lines 2 to 3 that it is particularly important for the photolytic cleaving off of protective groups to introduce a suitable substituent on the  $\alpha$ -C atom – corresponding to  $R^4$  in claims 1 and 29 of the present application. In an additional requirement according to Hasan et al, page 4250, last paragraph, it is important to introduce a suitable substituent in o-position on the ring.

In regard to substituents in the m- and p-positions on the ring of formula 1, Hasan et al, page 4247, Abstract, last sentence, teaches that “*In general, substitutions at other*

*positions on the phenyl ring had less effect on photolysis rates.*” According to Hasan et al, page 4250, lines 1 to 2, these results are in agreement with other scientific investigations.

In summary, it therefore follows from Hasan et al that the substituents at R<sup>4</sup> or in o-position on the ring must be optimized, and *that changes at R<sup>1</sup> and R<sup>2</sup> have no positive effect* (see Hasan et al, page 4247, Abstract, last sentence).

Against this background and the unequivocal teaching from Hasan et al, it was *not* obvious to introduce new substituents at R<sup>1</sup> and R<sup>2</sup>. To the contrary, Hasan et al even leads *away* from the present application, since it imparts to the person skilled in the art the impression that he must vary R<sup>4</sup> (in claim 1) or the o-position in the ring. He therefore would not have seen any “reasonable expectation of success” by varying the R<sup>1</sup> or R<sup>2</sup> position.

But even if this had not been taken into consideration, there is no kind of indication in Pfleiderer et al or Hasan et al as to what type of change, or in other words which substituents, must be introduced at R<sup>1</sup> and R<sup>2</sup> position in order to improve the effectiveness of photolytic cleavage of protective groups. The radicals R<sup>1</sup> and R<sup>2</sup> used according to claim 1 are not made obvious by Pfleiderer et al or Hasan et al.

Even Pfleiderer et al or Hasan et al in combination with Eritja et al do not lead to the present application. Thus no light-controlled method of oligonucleotide synthesis is disclosed in Eritja et al. To the contrary, Eritja et al disclose exclusively cleaving off protective groups with DBU (see page 4177, Conclusions, lines 8 to 13). This means that Eritja et al relates not to photochemistry but to a completely different technical field. Furthermore, the protective group from Eritja et al is described therein as not worthy of recommendation, on page 4177, lines 8 to 10.

In combination with the teaching from Hasan et al, or in other words that the  $\alpha$ -C atom must be appropriately substituted (Hasan et al, page 4251, lines 2 to 3 and Table 1), a

person skilled in the art would have rejected the protective groups according to compound No. 9 from Eritja et al as unsuitable, since therein two H atoms are bonded to the  $\alpha$ -C atom, which according to Hasan et al, page 4251, Table 1, is disadvantageous.

In summary, neither Pfleiderer et al or Hasan et al nor Eritja et al taken alone or in combination make obvious the inventive protective groups according to the claimed invention. To the contrary, Pfleiderer et al or Hasan et al leads – as demonstrated – away from the present application.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 1-17 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

Applicants wish to remind the Examiner that: “Applicants are their own lexicographer” (MPEP §2173.01). MPEP §2173.01 also states that Applicants “can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art.” Further, definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP §2173.02).

In view of the proper examination standard set forth above, Applicants offer the following comments in regard to the Examiner’s specific criticisms:

The claim limitation “*leaving group*” is clearly defined on page 12, lines 11-16 of the description. Which type of “leaving group” is used is not relevant to the art of the present



application. What is essential are the substituents  $R^1$ ,  $R^2$  and  $R^4$ , since they determine the photochemical properties. As such, it is therefore neither possible nor necessary to list explicitly all theoretically conceivable "leaving groups". Applicants submit that the definition of the term on page 12, lines 11-16 is sufficient to direct the skilled artisan to the meaning of this term and to envision the permissible structures/compounds for use in the present application.

In regard to the claim limitations "*a functional group useful in oligonucleotide synthesis*" and "*chemically modified*", the Examiner's attention is directed to the definition provided on page 12, line 22 to page 13, line 11. With respect to the relevance of these "functional groups" and "chemical modification", the explanation already given above for "leaving groups" is applicable by analogy.

Further, the claim limitation "*protective group*" is clearly defined on page 11, lines 4-14, and explicit examples are mentioned.

Finally, with respect to the claim limitation "analog thereof" reference is made to the definition provided at page 12, line 16 to page 13, line 11. Further, it should be noted that analogs of deoxyribonucleosides, ribonucleosides, deoxyribonucleotides, and ribonucleotides are well-known in the art. As such, the term "analog" within the context of the present application would be readily understood.

In view of the foregoing, Applicants submit that the claims are clear and unambiguous. As such, withdrawal of this ground of rejection is requested.

The rejection of Claim 13 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

The Examiner is again reminded of the standard set forth in MPEP §2173.01. Further, with respect to the “intermediate *OH-protective group*” in Claim 13, Applicants make reference to the definition provided for the “*protective group*” which is clearly provided at page 11, lines 4-14, and explicit examples are mentioned. Applicants submit that in view of this definition and the general knowledge in the art the claims are sufficiently clear so as to be definite.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 9-11 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Claims 9-11 have been amended to depend from Claim 1. As such, the criticisms in these claims have been obviated.

Withdrawal of this ground of rejection is requested.

The objection to Claims 9-11 under 37 C.F.R. §1.75(c) are obviated by amendment. Claims 9-11 have been amended to depend from Claim 1. As such, withdrawal of this ground of objection is requested.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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